What does the term Metabolic Syndrome describe?
Metabolic syndrome describes a cluster of cardio-metabolic conditions that increase one's risk of developing type 2 diabetes, stroke and heart disease. These cardio-metabolic conditions include:

- abdominal obesity
- hyperglycaemia (abnormally high levels of glucose in the blood)
- dyslipidaemia (abnormally high levels of fat – HDL, LDL, triglycerides and fatty acids - in the blood) and
- high blood pressure

Metabolic syndrome in and of itself is not a disease, it is a term used to classify and identify people's risk of developing type 2 diabetes, stroke and heart disease. People are classified as having metabolic syndrome when they have three or more of:

- central obesity (the exact link is not clear, but is has been proven that central obesity is a high risk factor)
- high blood pressure
- high levels of blood triglycerides
- low levels of HDL ('good cholesterol')
- impaired fasting glucose or diabetes. Impaired fasting glucose occurs when blood glucose levels are higher than normal but not high enough to be classified as type 2 diabetes.

Metabolic syndrome can result in type 2 diabetes. This means that the body does not use insulin as effectively as it should, especially in the muscles and liver. In a normal situation, carbohydrates are broken down to glucose and glucose passes through the intestines to the bloodstream. As the glucose levels in the blood increase, the pancreas secretes insulin to bloodstream. Insulin allows glucose to go into muscle cells from the blood, recovering the blood glucose level of before. Once glucose is inside the muscle cell, it is burned with oxygen to produce energy – ATP! When someone has insulin resistance, the pancreas needs to release more insulin to trigger the transport of glucose from the bloodstream to the muscle cells to maintain normal blood glucose levels. Consistently high blood glucose levels can damage organs.

Metabolic syndrome can result in heart disease and stroke. This is because increased triglyceride and reduced HDL cholesterol increase the risk of atherosclerosis. Atherosclerosis is the narrowing of the arteries, which makes it harder for blood to pass through and easier for circulation problems to occur. Fatty diets also result in artery plaques, which can obstruct blood flow. If the person also has plaque deposits in their arteries, this further increases the person's risk of CVD and stroke because it blood movement slows and is more likely to be obstructed.

Metabolic syndrome has also been known as Syndrome X, insulin resistance syndrome, dysmetabolic syndrome, multiple metabolic syndrome, deadly quartet and CHAOS.
syndrome.

What is disease clustering?
This refers to conditions that can arise from the same risk factors, and are likely to present together. For example: if conditions A, B and C all have obesity as a risk factor, an obese person is at risk of developing one or more of the conditions. If conditions A and/or B and/or C are risk factors for further conditions, it is likely that further conditions will develop.

Why is adipose tissue referred to as “sick fat”?
Adipose tissue is highly vascularised and metabolically active. It releases leptin, which is a hormone involved in the regulation of body fat. Leptin also interacts with the areas of the brain that control hunger and signals to the brain that the body has had enough to eat. Insulin also acts of adipose tissue. Adipose tissue is therefore able to communicate with itself and other tissues, because it is surrounded by fibrous connective tissues, collagen, nerves and blood vessels.

Adipose tissue is referred to as 'sick fat' (aka adipose-opathy) when it malfunctions. These malfunctions include abnormal enlargement of individual fat cells (hypertrophy; as opposed to increasing number of fat cells) as well as sending pathological signals to organs, especially in the endocrine and immune departments. Such pathogenic effects include promotion of atherosclerosis and endothelial dysfunction. These malfunctions can promote CVD and can cause or worsen metabolic syndrome. As many factor of metabolic syndrome are major CVD risk factors, sick fat therefore indirectly increases CVD risk.

Adiposopathy (“Sick Fat”): Summary of Causality and Examples of Anatomic, Pathophysiological, and Clinical Manifestations*

<table>
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<tr>
<th>Causes of adiposopathy</th>
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<tr>
<td>Sedentary lifestyle</td>
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<td>Genetic predisposition</td>
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<td>Environmental causes</td>
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<tr>
<th>Anatomic manifestations of adiposopathy</th>
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<td>Adipocyte hypertrophy</td>
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<td>Visceral, pericardial, perivascular, and other periorgan adiposity</td>
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<td>Growth of adipose tissue beyond its vascular supply</td>
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<td>Increased number of adipose tissue immune cells</td>
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<td>“Ectopic fat deposition” in other body organs</td>
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<td>Pathological adipocyte organelle dysfunction</td>
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<tr>
<td>Increased circulating free fatty acids</td>
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<td>Pathogenic adipose tissue endocrine responses (e.g., increased leptin, increased tumor necrosis factor-alpha, decreased adiponectin, and increased mineralocorticoids)</td>
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<tr>
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<tr>
<td>Pathogenic interactions or pathogenic cross talk with other body organs (e.g., liver, muscle, and central nervous system)</td>
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Adiposopathy ("Sick Fat"): Summary of Causality and Examples of Anatomic, Pathophysiological, and Clinical Manifestations

*Adiposity can result in both fat-mass pathology and fat dysfunctional abnormalities resulting in adiposopathy.

Causes of adiposopathy

- Positive caloric balance
- Sedentary lifestyle
- Genetic predisposition
- Environmental causes

Anatomic manifestations of adiposopathy

- Adipocyte hypertrophy
- Visceral, pericardial, perivascular, and other periorgan adiposity
- Growth of adipose tissue beyond its vascular supply
- Increased number of adipose tissue immune cells
- "Ectopic fat deposition" in other body organs

Pathophysiological manifestations of adiposopathy

- Impaired adipogenesis
- Pathological adipocyte organelle dysfunction
- Increased circulating free fatty acids
- Pathogenic adipose tissue endocrine responses (e.g., increased leptin, increased tumor necrosis factor-alpha, decreased adiponectin, and increased mineralocorticoids)
- Pathogenic adipose tissue immune responses (e.g., increased proinflammatory responses through increased tumor necrosis factor-alpha and decreased anti-inflammatory responses through decreased adiponectin)
- Pathogenic interactions or pathogenic cross talk with other body organs (e.g., liver, muscle, and central nervous system)

Clinical manifestations of adiposopathy

- Hyperglycemia
- High blood pressure
- Dyslipidemia
- Metabolic syndrome
- Atherosclerosis
- Fatty liver
- Hyperandrogenemia in women
- Hypoandrogenemia in men
- Cancer

The exact details are still under investigation.

Bays, 2011 [WEEK 1 EXTRA]

Describe the anatomical position of sick fat?
Sick fat is located centrally, around the abdomen.

What are the core pathological components of the Metabolic Syndrome used by most definitions?

1) Central obesity (waist circumference) (MAIN)
2) High glucose levels
3) high blood pressure
4) high blood triglycerides
5) reduced HDL cholesterol (good cholesterol)

What is a major issue associated with having several definitions of Metabolic Syndrome?
Misdiagnosing or mistreating because of the inconsistencies between definitions. Each definition has different cut-off points for waist measurements considered 'at-risk' (the measurements for Asian populations are smaller than for Anglo populations). Definitions differ between the American Diabetes Association and the European Association for the Study of Diabetes.

Other issues of metabolic syndrome definitions are:

1) everyone diagnosed with metabolic syndrome is treated the same way, no matter the number or combination of conditions that they have under the metabolic syndrome umbrella
2) relying on the clinical diagnosis only falls short of using a tape measure, which is easier, less invasive and cheaper than clinical tests and methods
3) different definitions can result in skepticism of the condition itself

Describe the hypothesised reason behind this clustering of diseases.
Chronic inflammation is thought to underlie the clustering of diseases that comprise metabolic syndrome. Inflammation is the immune system's response of sending white blood cells out to cellular injury; it's a protective and restorative response.

Chronic inflammation accompanies overweight and obesity. When a person gains fat tissue, the fat first fills the adipose tissue. When that is full, it then migrates to other tissues, such as muscles and the liver. The accumulation of fat, especially in the
abdominal region, changes the body's metabolism and inflammation develops. There are few immune cells (WBCs [macrophages]) in adipose tissue, so weight gain causes and increased number and therefore inflammation develops. This results in insulin resistance, low HDL, high triglycerides and high blood pressure. All of these symptoms are the metabolic syndrome.

**short-term**

1) TNFα
   - Prothrombotic and inflammation
   - increases vascular inflammation
     - decreases insulin sensitivity and insulin signalling
2) IL-6
   - Insulin resistance and dyslipidaemia
   - increases vascular inflammation
   - Decreases insulin signalling
     - Major regulator of hepatic CRP
3) CRP – assists compliment binding to damaged cells

**macrophage phagocytosis**
   - Prothrombotic and inflammation
   - Increases vascular inflammation
   - Correlates with metabolic syndrome and diabetes
4) PAI-1 (Plasminogen activator inhibitor-1)
   - Prothrombotic
   - SERINE protease inhibitor
   - Inhibits tissue plasminogen activator and urokinase
5) Leptin
   - Hypertensive
   - Major long term satiety signal (flip side is probably more true)
   - Subcutaneous rather than visceral fat is the major producer
6) Angiotensinogen
   - Hypertension
   - Adipocytes are the major source after the liver
   - Expressed more in visceral adipocytes than in subcutaneous
7) Resistin
   - Insulin resistance
     - Decreases anti-inflammatory effect
TOPIC 2: HYPERTENSION

What are the determinants of blood pressure in the body? How is blood pressure measured?

a) There are numerous determinants of blood pressure in the body:
   - physical activity
   - sympathetic nervous system
   - width and flexibility of arteries
   - emotions: anger and fear
   - body temperature
   - age (vessels are made of muscle and muscle stiffens with age)
   - gender
   - vasodilator symptoms
   - renin-angiotension system
   - vasoporessin
   - endothelial factors

b) Blood pressure is measured using a sphygmomanometer. It is an inflatable cuff wrapped around the forearm. It inflates to briefly interrupt the blood flow in the main artery and then deflates to restore it. A stethoscope is used to listen for Korotkoff sounds as the blood begins to flow again in the artery.

Blood pressure is measured in a fraction format: 120/80. The top number is systolic blood pressure (SBP) and this number refers to the force of blood on the arteries when the heart beats (i.e., the highest blood pressure with each heart beat).

The bottom number is diastolic blood pressure (DBP) and this refers to the force of blood on the arteries between beats, aka the resting pressure of the circulatory system (i.e., the lowest pressure).

Define hypertension. Understand the causes, prevalence and risk to health of hypertensive individuals.

a) Hypertension means that the blood is pumping at a higher pressure than normal through the arteries. It is clinically defined as being greater than or equal to 140/90 mmHg. There are classifications of hypertension for adults:

<table>
<thead>
<tr>
<th>BP Category</th>
<th>Systolic mm Hg</th>
<th>Diastolic mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>And &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120 – 139</td>
<td>Or 80 - 89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140 – 159</td>
<td>Or 90 - 99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>Or ≥100</td>
</tr>
</tbody>
</table>

Prehypertensive people are targeted for lifestyle changes.

b) There are many causes of hypertension:
   - genetics
   - age (arteries harden and stiffen with age)